

HUNZIKER 2661-2662

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J2662-m1

7-(2'-Deoxy-3',5'-di-O-benzoyl- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine

To a suspension of 25.70 g (72.1 mmol) methyl 3,5-di-O-benzoyl-2-deoxy- α,β -D-*erythro*-pentofuranoside and 11.50 g (48.1 mmol) N²-isobutyryl-guanine hydrate in 250 mL abs. CH₃CN under argon was added 58.9 mL (49.2 g, 241.4 mmol) N,O-bis(trimethylsilyl) acetamide. After stirring for 8 hrs at room temperature a clear solution was formed and 16.9 mL (37.5 g, 144.0 mmol) SnCl₄ was added dropwise within 20 min. Stirring was continued for 12 hrs at room temperature. Then the reaction mixture was poured on 800 mL CHCl₃ and washed with water (800 mL) and saturated aqueous NaHCO₃ (2 x 800 mL). The aqueous layers were reextracted with 400 mL CHCl₃. The combined organic phases were dried (Na₂SO₄) and evaporated. The remaining oil was flash chromatographed on 600 g silica gel with ethyl acetate and then twice on 600 g silica gel with toluene/acetone 7:3 which gave 2.64 g (4.84 mmol, 10%) pure 7-(2'-deoxy-3',5'-di-O-benzoyl- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine. TLC: EtOAc (R_f = 0.27).

¹H NMR (300 MHz, CD₃OD-*d*₄): 12.44 (s, br., 1 H, H-N(1)), 10.65 (s, br., 1 H, H-N(2)), 8.19 (s, 1 H, H-C(8)), 7.99 - 8.10 (m, 4 H, CH-Bz), 7.17 - 7.63 (m, 6 H, CH-Bz), 6.77 - 6.79 (m, 1 H, H-C(1')), 4.69 - 4.71 (m, 1 H, H-C(3')), 4.75 - 4.78 (m, 1 H, H-C(4')), 2.99 - 3.05 (m, 2 H, H-C(5')), 2.85 (m, 1 H, CH-ⁱPr), 2.22 - 2.36 (m, 1 H, H-C(2')), 1.23 (d, J = 6.8 Hz, 3 H, CH₃-ⁱPr), 1.21 (d, J = 6.8 Hz, 3 H, CH₃-ⁱPr).

J 2662-m2

7-(2'-Deoxy- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine

A solution of 2.64 g (4.84 mmol) of 7-(2'-deoxy-3',5'-di-O-benzoyl- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine in 193 mL THF/ MeOH/ water 5:4:1 was cooled to 0°C. Then 19.3 mL of a 2 M aqueous NaOH solution was added. After stirring for 25 min at 0°C the reaction was quenched by addition of 2.49 g (46.6 mmol, 1.2 mol-equiv. rel. to NaOH) ammonium chloride and stirring was continued for 15 min. Then the solution was evaporated. The remainder was flash-chromatographed on 190 g silica gel with CH₂Cl₂/MeOH 6:1 which gave 1.35 g (4.00 mmol, 83%) of 7-(2'-deoxy- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine. TLC: CH₂Cl₂/MeOH 6:1 (R_f = 0.29).

¹H NMR (300 MHz, DMSO-*d*₆): 11.85 (s, br., 2 H, H-N(1,2)), 8.47 (s, 1 H, H-C(8)), 6.48 - 6.53 (m, 1 H, H-C(1')), 5.30 - 5.33 (m, 1 H, H-O(3')), 4.97 (t, J = 5.4 Hz, 1 H, H-O(5')), 4.15 - 4.32 (m, 1 H, H-C(3')), 3.83 (m, 1 H, H-C(4')), 3.41 - 3.60 (m, 2 H, H-C(5')), 2.62 - 2.76 (m, 2 H, H-C(2'), CH-ⁱPr), 2.19 - 2.34 (m, 1 H, H-C(2')), 1.09 (d, J = 6.8 Hz, 6 H, CH₃-ⁱPr).

J2662-m3

7-(2'-Deoxy-5'-O-[bis(4-methoxyphenyl)phenylmethyl]- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine

To a solution of 501 mg (1.49 mmol) of 7-(2'-deoxy- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine in 15 mL abs. pyridine under argon was added 604 mg (1.78 mmol, 1.2 mol-equiv.) 4,4'-dimethoxytrityl chloride. This solution was stirred for 4 hrs at room temperature. Then the reaction mixture was diluted with 100 mL CH₂Cl₂ and washed with saturated aqueous NaHCO₃ (2 x 50 mL). The aqueous layers were back extracted with 50 mL CH₂Cl₂. The combined organic phases were dried (Na₂SO₄) and evaporated. The remaining oil was flash chromatographed on 120 g silica gel with 4% MeOH in CH₂Cl₂ to give 688 mg (1.08 mmol, 73%) 7-(2'-deoxy-5'-O-[bis(4-methoxyphenyl)phenylmethyl]- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine as a yellow foam. TLC: 4% MeOH in CH₂Cl₂ (R_f = 0.27).

¹H NMR (300 MHz, CDCl₃): 12.49 (s br., 1 H, H-N(1)), 10.36 (s br., 1 H, H-N(2)), 8.14 (s, 1 H, H-C(8)), 7.40 (m, 2 H), 7.14 - 7.34 (m, 7 H), 6.78 - 6.81 (m, 4 H), 6.72 (t, J = 6.1 Hz, 1 H, H-C(1')), 4.58 (m, 1 H, H-C(3')), 4.46 (d, 1 H, H-O(3')), 4.28 (m, 1 H, H-C(4')), 3.75 (s, 6 H), 3.40 (m, 2 H, H-C(5')), 2.88 - 3.04 (m, 2 H, H-C(2'), CH-ⁱPr), 2.50 (m, 1 H, H-C(2')), 1.26 (d, J = 6.8 Hz, 3 H, CH₃-ⁱPr), 1.25 (d, J = 6.8 Hz, 3 H, CH₃-ⁱPr).

J2662-m4

^{13}C NMR (75 MHz, CDCl_3): 180.2 (s, CO- $i\text{Bu}$), 158.6 (s, C-PhOMe), 157.9 (s, C(4)), 153.1 (s, C(6)), 147.8 (s, C(2)), 144.6 (s, C-Ph), 141.1 (d, C(8)), 135.7 (s, CH-PhOMe), 135.6 (s, CH-PhOMe), 130.1 (d, CH-PhOMe), 128.1 (d, CH-Ph), 128.0 (d, CH-Ph), 127.0 (s, C-PhOMe), 113.3 (d, C-PhOMe), 111.1 (s, C(5)), 87.6 (d, C(1')), 86.8 (s, C-DMT), 86.7 (d, C(4')), 72.0 (d, C(3')), 63.8 (t, C(5')), 55.3 (q, $\text{CH}_3\text{-PhOMe}$), 43.1 (t, C(2')), 36.2 (d, CH- $i\text{Pr}$), 19.2 (q, $\text{CH}_3\text{-}i\text{Pr}$), 19.1 (q, $\text{CH}_3\text{-}i\text{Pr}$).

MS (FAB, NBA): 640 (1), 304 (24), 303 (100), 222 (15), 152 (11), 135 (5).

HR-MS: 640.2755 (calcd. for $\text{C}_{35}\text{H}_{38}\text{N}_5\text{O}_7$ (MH^+): 640.2771)

**7-(2'-Deoxy-5'-O-[bis(4-methoxyphenyl)phenylmethyl]-3'-O-[[2-cyanoethoxy]
[diisopropylamino]phosphino]- β -D-erythro-pentofuranosyl)-N²-isobutyryl-guanine**

2-Cyanoethyl *N,N*-diisopropylchlorophosphoramidite (138 mL, 147 mg, 0.620 mmol) was added dropwise under argon to a solution of 264 mg (0.413 mmol) 7-(2'-deoxy-5'-O-[bis(4-methoxyphenyl)phenylmethyl]- β -D-erythro-pentofuranosyl)-N²-isobutyryl-guanine and 212 mL (160 mg, 1.24 mmol) diisopropylethylamine in 4 mL abs. THF. After stirring for 1 hr at room temperature the reaction mixture was diluted with 100 mL CH_2Cl_2 and washed with cold saturated aqueous NaHCO_3 (2 x 50 mL). The aqueous layers were reextracted with 50 mL CH_2Cl_2 . The combined organic phases were dried (Na_2SO_4) and evaporated. The remaining oil was immediately flash chromatographed on 90 g silica gel with CH_2Cl_2 /acetone 7:3 to

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give 271 mg (0.323 mmol, 78%) 7-(2'-deoxy-5'-O-[bis(4-methoxyphenyl)phenyl-methyl]-3'-O-[[2-cyanoethoxy][diisopropylamino]phosphino]- β -D-*erythro*-pentofuranosyl)-N²-isobutyryl-guanine as a brittle colorless foam. TLC: CH₂Cl₂/acetone 7:3 (R_f = 0.57, 0.52 (2 diastereomers)).

¹H NMR (300 MHz, CDCl₃): 12.29 (s br., 1 H, H-N(1)), 10.04 (s br., 1 H, H-N(2)), 8.15 (s, 0.5 H, H-C(8)), 8.11 (s, 0.5 H, H-C(8)), 7.42 (m, 2 H), 7.19 - 7.34 (m, 7 H), 6.79 - 6.86 (m, 4 H), 6.67 (t, J = 6.2 Hz, 1 H, H-C(1')), 4.63 (m, 1 H), 4.29 (m, 1 H), 3.38 - 3.91 (m, 6 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.44 - 2.95 (m, 5 H), 1.09 - 1.27 (m, 18 H).

MS (FAB, NBA): 840 (1), 304 (24), **303** (100), 222 (8), 201 (7), 152 (6).

HR-MS: 840.3857 (calcd. for C₄₄H₅₅N₇O₈P (MH⁺): 840.3850)